

Examiner Interview

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Solid Oral Dosage Form Containing an Enhancer
U.S. Patent Application No. 09/510,560

Pharmaceutical Development

- ❑ Drug must be in solution to be absorbed
- ❑ Products mature from liquids to solids
 - ❖ Elixirs were earliest dosage forms.
 - ❖ Pills were created by mixing liquids with excipients, forming wet masses which were allowed to dry
- ❑ First human dosage forms are almost always powder for reconstitution or solution
 - ❖ Using solutions is a more simplistic approach
 - ❖ Easier to formulate with small amounts of material
 - ❖ Avoids issue of getting drug to an absorbable state

Pharmaceutical Development

- Dosage Form Preference
 - ❖ Tablets are preferred over capsules
 - ❖ Powder filled capsules are preferred over liquid filled capsules
 - ❖ Liquid filled capsules are preferred over free flowing liquids

Pharmaceutical Development

- ❑ Advantages of solid forms
 - ❖ Solid state stability is better than solution state
 - ❖ Tableting is the simplest and fastest pharmaceutical process
 - ❖ Tablets have the longest shelf life
 - ❖ Tamper evidence is greatest with tablets
 - ❖ Accuracy of dosing is greatest with solids
 - ❖ Shipping costs are lowest

Market Preference for Solid Forms

- ❑ Of the top 50 products in 2005:
 - ❖ 22 are available only as tablets
 - ❖ 2 are available only as capsules
 - ❖ 3 are available only as tablets and capsules
 - ❖ 27 products are available only as tablets or capsules
 - ❖ 12 are only available as injectables

Drug Enhancer Technology

- ❑ Drug delivery techniques also mature from liquids to solids
 - ❖ Transdermals
 - ❖ Intranasals/inhalations
 - ❖ Poorly permeable oral compounds

Drug Enhancer Technology

- Transdermals
 - ❖ Initial systems were liquids in pouches or gels (Key nitroglycerin (NTG), Ciba NTG, Ciba estradiol (E2); all introduced in the 80's)
 - ❖ Current marketed products are all soluble in the adhesive systems (NTG, E2, nicotine, fentanyl, clonidine, norethindrone, scopolamine, testosterone)
 - ❖ Liquid systems were developed for other products but never commercialized
 - ❖ Few drugs have sufficient solubility in medical grade adhesives
 - ❖ New technologies in development to allow other drugs to be delivered (microporation, iontophoresis)

Drug Enhancer Technology

- ❑ Intranasals/inhalations
 - ❖ No powder intranasals are marketed yet, though delivery devices are available
 - ❖ First insulin inhalation product dependent on development of powder technology

Drug Enhancer Technology

- ❑ Poorly permeable oral compounds
 - ❖ Digoxin absorption improved by a liquid filled capsule (1982)
 - ❖ Cyclosporine is a poorly permeable peptide
 - Was initially marketed in 1983 as an injectable and an oral liquid
 - Was marketed in 1990 as liquid-filled soft gel capsule
 - Was marketed in 1995 as a microemulsion based liquid and liquid filled capsule
 - Set a standard for emulsion-based systems

Drug Enhancer Technology

- ❑ Poorly permeable oral compounds (con't)
 - ❖ Merrion is an innovator in microemulsion liquid systems to deliver poorly permeable compounds:
 - US 5,633,226 (97), surfactants, lipids, fatty acid salt
 - US 5,444,041 (97), surfactants, lipids, fatty acid salt
 - US 5,646,109 (97), surfactants, lipids, fatty acid salt
 - US 5,688,761 (97), surfactants, lipids, other components may be present
 - US 5,707,648 (98), surfactants, lipids, PEG
 - No products have been commercialized using any of these technologies
 - The current technology was developed to overcome issues with these systems

Drug Enhancer Technology

- ❑ Poorly permeable oral compounds (con't.)
 - ❖ Starch capsules developed in part to meet need for shells compatible with surfactants
 - ❖ Sirolimus (rapamycin) was initially marketed as liquid dosage form and is now available as a tablet using nanocrystal technology
 - Patent 5,559,121 (1996) discloses oral sirolimus compositions; only has liquid examples
 - Sirolimus patent 5,536,729 (1996) has oral liquid and starch capsule examples

Cited References

- Bachynsky et al. (U.S. Patent No. 5,190,748)
 - ❖ Compositions composed of emulsifiable systems of surfactants and lipids which are liquids or low melting point solids used to form liquids which are poured into capsules
 - ❖ Compositions do not require drug solutions, but use surfactants to facilitate solubility in systems that are liquid at the administration site

Cited References

- Fujii et al. (U.S. Patent No. 5,840,685)
 - ❖ Uses surfactant-based systems that are liquid at or below body temperature to deliver antibiotics vaginally
 - ❖ Discloses MCFA salts only in two-component enhancer systems in combination with other materials

Cited References

- ❑ Watts et al. (WO 97/05903)
 - ❖ Surfactants are used to form microemulsion-like systems that are liquid at or below body temperature.
 - ❖ All the examples use only starch capsules. The assignee bought the starch capsule technology from Warner-Lambert when they discontinued development. This technology has not been commercialized.
 - ❖ Most of the formulae disclosed in Watts are not compatible with commercially available capsules.
 - ❖ Additionally, they cannot be formed into tablets.